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Proceedings of the Military mTBI Diagnostics Workshop, St. Pete Beach, August 2010

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Abstract

Approximately 28,000 service members (SMs) sustain a traumatic brain injury (TBI) each year in the U.S. military. The majority of the injuries result either in a brief or no loss of consciousness, and are classified as a mild TBI (mTBI or concussion). Current evaluation guidelines of SMs suspected of having a mTBI rely heavily on self-reports. However, there is concern that SMs typically minimize or do not report their symptoms of mTBI for fear that doing so will result in being removed from the battlefield. Because mTBI often results in headaches, cognitive dysfunction, attention difficulties, and balance problems, returning to the battlefield before resolution of their symptoms can be dangerous for the SM and for their unit. Sustaining a second concussion before resolution of a previous mTBI also may make long-term neuronal injury more likely. The mTBI Diagnostics Workshop was designed as a forum where civilian and military experts from a variety of TBI-related clinical and basic science disciplines could meet to define the diagnostic tools, alone or in combination, that were most likely to result in an acute, objective diagnosis of mTBI. The premise of the meeting was that a small number of well-focused research projects conducted over the next 2–3 years could be done to validate the optimal test, or more likely combination of tests, that would be practical and reliable for the acute diagnosis of mTBI within 2–3 h of injury in theater. The recommendations of the Workshop are provided in this report.

Key words: concussion; diagnosis; mild traumatic brain injury; Neurocognitive Assessment Tool (NCAT); Military Acute Concussion Evaluation (MACE); Operation Iraqi Freedom (OIF); Operation Enduring Freedom (OEF); military mild traumatic brain injury

Introduction

During the last 10 years more than 179,000 active duty United States service members (SMs) have sustained a traumatic brain injury (TBI), according to data collected from medical records and analyzed by the Defense and Veterans Brain Injury Center (DVBIC) in cooperation with the Armed Forces Health Surveillance Center (AFHSC) (Defense and Veterans Brain Injury Center/Armed Forces Health Surveillance Center, 2010). However, this number may not include many of those with a concussion, because like many athletes, SMs who have a concussion often ignore or deny their symptoms so that they will be allowed to return to duty. A Rand Corporation survey of veterans who have returned from Afghanistan or Iraq found that 19.5%, or nearly 380,000 SMs, reported possibly having sustained a TBI while deployed (Tanielian et al., 2008).

Common acute symptoms of concussion include headaches, cognitive dysfunction associated with attentional deficits, dizziness, and balance or vestibular dysfunction.(Broglio and Puetz, 2008). Returning to combat before resolution of these symptoms and signs of a concussion or mild TBI (mTBI) could be hazardous for the SM, and for other members of the unit, because the SM may not be able to sight their weapon accurately, respond to orders quickly, or properly function in a variety of other mission-critical ways. Moreover, there is clinical evidence that the brain may be metabolically vulnerable for days after the trauma (Bergsneider et al., 2001; Giza and Hovda, 2001), and a second impact during that time may result in prolonged or permanent damage (McCrea et al., 2004). In some cases at least, the behavioral, psychological, and physical symptoms associated with concussion that are increasingly observed among returning SMs may very well be due to a second injury before full recovery from the first.

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14. ABSTRACT

Approximately 28,000 service members (SMs) sustain a traumatic brain injury (TBI) each year in the U.S. military. The majority of the injuries result either in a brief or no loss of consciousness, and are classified as a mild TBI (mTBI or concussion). Current evaluation guidelines of SMs suspected of having a mTBI rely heavily on self-reports. However, there is concern that SMs typically minimize or do not report their symptoms of mTBI for fear that doing so will result in being removed from the battlefield. Because mTBI often results in headaches cognitive dysfunction, attention difficulties, and balance problems, returning to the battlefield before resolution of their symptoms can be dangerous for the SM and for their unit. Sustaining a second concussion before resolution of a previous mTBI also may make long-term neuronal injury more likely. The mTBI Diagnostics Workshop was designed as a forum where civilian and military experts from a variety of TBI-related clinical and basic science disciplines could meet to define the diagnostic tools, alone or in combination, that were most likely to result in an acute, objective diagnosis of mTBI. The premise of the meeting was that a small number of wellfocused research projects conducted over the next 2?3 years could be done to validate the optimal test, or more likely combination of tests, that would be practical and reliable for the acute diagnosis of mTBI within 2?3 h of injury in theater. The recommendations of the Workshop are provided in this report.

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Currently the diagnosis of concussion relies primarily on information volunteered by the SM. Self-report is a key part of the military clinical practice guideline for mTBI diagnosis during the field evaluation performed by combat medics and corpsmen. This guideline prescribes a standardized initial evaluation using the Military Acute Concussion Evaluation (MACE), a three-part examination developed by McCrea and colleagues around the Standardized Assessment of Concussion (Barr and McCrea, 2001; McCrea et al., 2003). However, this method of diagnosis must be considered suspect, because military culture is such that SMs may be reluctant to volunteer symptoms of a TBI if they think that doing so will result in their being removed from the mission. In some cases SMs also believe that any symptoms they divulge may result in a psychiatric diagnosis, which will negatively impact their career and/or security clearance.

There is an urgent need to identify a diagnostic test battery that will reliably provide an objective diagnosis of concussion soon after the trauma, and that is independent of the service member's self-report. The mTBI Diagnostics Workshop was conceived based on the premise that gaps currently exist in our understanding of the best methods for the acute, objective diagnosis of mTBI. Research in this area has been supported by the U.S. Army Medical Research and Materiel Command (MRMC) for more than 15 years. In 2009 a working group at MRMC assessed over 60 diagnostic modalities and identified 18 noninvasive diagnostic and/or monitoring technologies that might eventually be considered for use in theater for the acute diagnosis of mTBI. The conclusions of that working group were that the heterogeneity of TBI, especially mTBI, was such that it was unlikely that a single diagnostic test or device would emerge as capable of diagnosing mTBI. However, it was also recognized that the state of the knowledge was such that completion of a small number of well-defined, brief, research projects was likely to reveal a combination of diagnostic tests that could provide for the improved acute diagnosis of mTBI.

In order to define a small number of research projects that were most promising, we invited a group of civilian and military subject matter experts from medical and basic science disciplines related to mTBI to deliberate for 2 days and develop recommendations for research necessary to fill the remaining gaps in our understanding of what these optimal diagnostic tests are.

Meeting Format

Planning for this workshop began in February of 2010 with development of the agenda, and selection of 15 civilian subject matter experts (SMEs) from the entire spectrum of concussion-related clinical and research disciplines, and active duty military SMEs from the Army, Navy, and Air Force. SMEs were informed that the goal of the workshop was to describe accelerated and focused research projects that could identify the most promising, objective modalities or combinations of modalities for the diagnosis of mTBI that could be translated into field use in the next 2–3 years. They were provided six key references: the Department of Defense consensus statement on the definition of mTBI (Casscells, 2007), current management algorithms for mTBI used by the military (mTBI Working Group, 2009), a World Health Organization paper on TBI prognostics (Carroll et al., 2004), a paper on the multimodal assessment of sports concussion (Ellemberg et al., 2009), a paper describing the hurdles of developing point-of-care devices (Giljohann and Mirkin, 2009), and a report of an international consensus conference on concussion in sport (McCrory et al., 2009).

In addition, a list of clinical and imaging domains, and examples of tests of those domains, was provided to stimulate the SMEs to begin thinking about novel diagnostics or combinations of diagnostic tools prior to the meeting.(Table 1).

A 2-day meeting was designed, with the majority of the meeting dedicated to breakout sessions that allowed independent deliberation by small groups of SMEs. To stimulate scientific focus on the topic, the first session of the meeting was a series of brief presentations by each SME about their research, as specifically related to the acute diagnosis of mTBI. At the conclusion of their presentations each SME was also asked to describe what they saw as the most promising diagnostic tool that was not in their own area of research. The SMEs were then divided into three breakout groups and charged with refining the ideas and conceptualizing suitable research projects to validate the most appropriate modality, or combination of modalities, for the acute assessment of mTBI. To coordinate the work of the individual breakout groups, senior TBI experts from the Defense Centers of Ex-

Table 1. Clinical Categories and Examples of Diagnostic Tests That Might Be Considered for the Acute Diagnosis of Mild Traumatic Brain Injury

Physiologic/imaging domains	*Tests*
Electrophysiology	Brainscope Ahead M-100
Cognitive Assessment	MACE, ANAM, ImPACT
Autonomic	Pupillometry; heart rate variability assessment
Vestibular	Balance error scoring system (BESS); Rhomberg; vestibulo-ocular reflex (VOR)
Attention	Smooth pursuit eye tracking (Eye Trac)
Oculomotor	Saccades; smooth pursuit
Molecular biomarkers	Serum/blood biomarkers; peripheral white blood cell gene expression; saliva; urine; microfluidics; nanotechnology
Imaging (vascular instability)	Transcranial Doppler; hemodynamic vascular analysis (e.g., New Health Sciences, Inc.)
Imaging (structural)	Transcranial ultrasound (shear mode, C-scan, vibroacoustics, and other approaches)
Imaging (functional and structural)	Near-infrared imaging
Cranial nerve function	Olfaction; oculomotor
Physical examination findings	Neurological soft signs (two-point discrimination); structured clinical interview

MACE, Military Acute Concussion Evaluation; ANAM, Automated Neuropsychological Assessment Metrics; ImPACT, Immediate Post-Concussion Assessment and Cognitive Testing.

Table 2. Script for Breakout Groups

1. An opening statement of purpose: "We are not trying to reach consensus on what the actual test or combination of tests are. Instead, we are looking for 5–7 research projects that could be completed in no more than 2–3 years, and would fill significant gaps in our current understanding of the objective field (theater) diagnosis of concussion."
2. Responses to presentations.
3. What was not mentioned by the presentations (gaps)?
4. What about newest technologies, such as microfluidics or nanotechnology?
5. What is mild traumatic brain injury (concussion)? What is the current gold standard for the diagnosis of concussion?
6. What is likely to be the best combination of diagnostic tests for the acute field diagnosis of concussion?
7. Of the recommended tests or combination of tests, what is likely to be the best of the best for the acute field diagnosis of concussion?
8. What research needs to be done to validate those tools?
   a. What role does a structured interview play as a validation tool?
   b. Can a particular imaging study or group of imaging studies be reliably used to validate a field-deployable combination of tests?
9. What other types of tools should be considered for the validation of candidate field-deployable diagnostic panels?
10. What is "plan B" if they fail the validation test?
11. How can we maximize available clinical resources to assure completion of the study within 2 years?

cellence for Psychological Health and TBI (DCoE), the DVBIC, and the National Institutes of Health (NIH) served as moderators, and TBI/education experts from DVBIC and DCoE served as scribes, for each of the three groups. Each of the moderators organized the deliberations of their groups by following the same script (Table 2). During the afternoon of the second day of the Workshop, a spokesperson for each breakout group presented their conclusions to an audience of military and other federal stakeholders.

Findings of the Workgroup

General considerations

The need for the discovery of an early diagnostic tool or combination of tools was further clarified, and considered important for addressing four specific issues:

- Diagnosis of mTBI: Has there been a concussion?
- Return to duty (RTD): Is the SM able to perform their duties or is there an additional risk of injury if the SM returns to duty?
- Treatment: Is there a need for immediate evacuation and/or intervention?
- Post-deployment treatment: Will there be a need for delayed intervention?

Two specific research mandates were emphasized: (1) development of tests that are able to detect brain injury, thereby determining biological validity, and (2) determination of the utility of each test (both current and new tests), either alone or in combination, and how they perform in the environment in which they will be used. During the conduct of research in theater it will be important to obtain interim, ongoing feedback from the field providers to determine the feasibility and utility of each candidate test, which must be useful at the medic/corpsman level.

Performance of any diagnostic test is dependent upon the population in which it will be used. Pre-test probability of a test result is a major influence on false-positive/false-negative rates. It is critical that the control population in the test development/validation process is as close as possible to the population in which it will be used. For example, the quality of data may be heavily influenced by the environment in which the test is being used, so the utility of the diagnostic test is dependent upon the actual medical decision-making environment. Exertional testing should be performed in an austere setting. Moreover, no single test is likely to provide the sensitivity and specificity that is required, and a complementary combination of tests has the most promise for improved diagnostic accuracy (Ellemberg et al., 2009; Guskiewicz et al., 2004; Tisdall and Smith, 2007).

The current gold standard for mTBI diagnosis

There is no universally recognized gold standard for the definition of mTBI, nor is there a gold standard diagnostic modality. The U.S. Department of Defense (DoD) has officially defined mTBI as trauma to the head associated with loss of consciousness for 30 min or less, alteration of consciousness for a moment up to less than 24 h, or post-traumatic amnesia for 24 h or less.(Casscells, 2007). SMs suspected of sustaining a TBI currently undergo acute evaluation with the MACE tool, and are presumed to have a TBI if they have a head injury, and related to that injury have some alteration of consciousness or loss of consciousness.

There was general agreement that at present, the gold standard against which any new single or combination diagnostic modality should be compared must include a standardized evaluation for mTBI. This should include a structured interview, detailed neurological assessment, and a test that would provide an objective biomarker of TBI. At present, magnetic resonance imaging (MRI), specifically diffusion tensor imaging (DTI), may be the best available modality for providing an imaging biomarker, although it remains an emerging technology.(Holli et al., 2010a, 2010b; Niogi and Mukherjee, 2010). Blood protein biomarker levels, neuropsychological assessments, and electrophysiological studies, also have proponents as potential gold standards for a definitive clinical diagnosis, but none are as close to clinical application as the imaging studies. Eventually any of these studies must be shown to correlate well with post-mortem pathology, or at least the characteristic clinical symptoms and signs of mTBI, to be universally accepted as the gold standard.

Diagnostic tools most appropriate for evaluation

A broad spectrum of diagnostic tests were carefully considered, and potential advantages and disadvantages of each test were discussed. There was general agreement that a combination of three or more tests of brain structure and function held the most promise for an objective, field-deployable test with a high degree of validity (Table 3).

If blood, urine, or salivary biomarkers are to be valuable for the early diagnosis of mTBI, they should reliably predict brain injury at the cellular level. Some molecular biomarkers are released very early after brain injury, while others may not appear until 24–48 h after the injury. Clearly those biomarkers

Table 3. Candidate Diagnostic Tests

Diagnostic test	*Positives*	*Concerns*
Military Acute Concussion Evaluation (MACE)	The current diagnostic algorithm used by the military	Not validated, though the Standardized Assessment of Concussion (SAC) portion of the MACE was validated in civilians (McCrea et al., 2003), though a clinical study for norming of later versions of the MACE is currently ongoing
Sport Concussion Assessment Tool–Second Edition (SCAT2; McCrory et al., 2009)	Comprised of the SAC, a quasi-neurological exam that is slightly more standardized than the MACE, a symptom rating section that is more of a continuum, and a balance test	SCAT2 requires considerably more time than the MACE to complete
Neurocognitive Assessment Tool (NCAT; e.g., Automated Neuropsychological Assessment Metrics [ANAM], Immediate Post-Concussion Assessment and Cognitive Testing [ImPACT])	ANAM has been in use by the Department of Defense (DoD) for 3 years, with over 615,000 pre-deployment studies completed; inter-individual variation can be accommodated with comparative pre-deployment test data	Requires analysis to see how to use this information; it also needs validation in-theater to determine the change associated with mild traumatic brain injury (mTBI); outcomes are independently influenced by environmental factors, especially sleep deprivation
Balance error scoring system (BESS; Iverson et al., 2008)	Foam plate on which the subject have to balance; easy-to-use scoring system; could be moved quickly to the field; a postural stability test is a high priority to consider, particularly with respect to performance of the service member's duties	There are a few portable tests used in research, but they may need more work to make the field-ready; sensitivity of the BESS to symptomatic mTBI is not yet adequately studied
Vestibulo-ocular reflex (VOR)	Tests the ability to keep focus on a target as the head moves; it could be automated and computerized techniques are under development; it is portable, quantitative, and requires minimal subject cooperation	Needs validation in theater and civilian mTBI; the test is not capable of differentiating mTBI from damage to vestibular nerves or the peripheral vestibular apparatus; thus it is not necessarily brain-specific
Ocular tracking task and smooth pursuit eye movement; saccades and antisaccades	Can measure a variety of different outputs of the brain, including attention and working memory; ocular movements can be tracked and quantified according to speed, direction, and delay; it is portable, quantitative, and requires minimal subject cooperation	Needs validation in theater and civilian mTBI; requires at least one intact, functional eye to be useful; sleep deprivation and stress can confound results
Olfaction testing	Easy to do; a person smells a card and is asked to identify the smell; olfaction is impaired in a large proportion of people affected by head injuries	The association of olfactory injury with mTBI is not clear; damage to olfaction can be caused by other exposure, such as chemical exposure
Quantitative electroencephalogram (EEG)	Certain EEG changes could be a signature of mTBI, but they would need to be well defined; a simplified cap-based system with a highly automated detection analysis system has been developed	There are concerns about obtaining a good signal-to-noise ratio (SNR) in the field, as it has a strong potential for high noise in the field versus a very small

(*continued*)

Table 3. (Continued)

Diagnostic test	*Positives*	*Concerns*
		electrical signal; sleep deprivation and diet also can affect EEG, along with external 60-cycle interference; there is a need to validate a well defined mTBI signature
Event-related potentials (ERPs)	Both auditory and visual (strobe) ERPs have been shown to be abnormal with mTBI; currently used for patients in a vegetative state to help predict the likelihood of regaining consciousness; an ERP device for medic use has been developed	Need to refine a field-deployable test; need to validate ERPs in mTBI, and to determine if mTBI is associated with a well-defined signature; maximizing the SNR and avoiding artifact is a primary concern for the acquisition of good-quality, interpretable data
Near-infrared spectroscopy (NIRS; van Rossem et al., 1999)	NIRS can be used to detect abnormal patterns of metabolic activity similarly to functional magnetic resonance imaging (fMRI), and for detecting superficial hemorrhage; easy-to-use devices are available and being used in studies of hemorrhage and task-related brain activation	Validation for use in the detection of metabolic changes characteristic of mTBI is the challenge
Heart rate variability	An automation and analysis package of heart rate variability could be used as a test of autonomic instability commonly associated with acute mTBI	Not a very specific finding and would need to be validated in an mTBI population, most likely as a component of a test battery
Pupillometry	An alternative test of autonomic instability that would require an automation and analysis package	Must be validated in an mTBI population; can also be affected by injury or compression of cranial nerves II or III
Imaging	Head-only MRI is under development and could be used for diffusion tensor imaging (DTI), or conventional imaging, at forward-theater medical treatment facilities; a portable head-only computed tomography (CT) device is currently available; since the average time for medical evacuation of injured service members is estimated at 53.3 min (according to a senior DoD official), such imaging in-theater may now be practical	Safety is the primary concern; up to 40% of neurotrauma cases cannot have an MRI because of retained metal fragments; a second concern is logistics, given the size and weight of these scanners; in addition, 8% of MRIs in normal subjects with no history of TBI are positive for mTBI-like lesions with T2-weighted protocols; therefore, baseline testing of service members at high risk of sustaining a TBI might need to be considered
Energy sensors (e.g., blast or impact dosimeters)	Detection of the degree and direction of mechanical energy exposure would be extremely helpful, especially if the data could be transmitted in real time to a laptop or personal digital assistant; prototype devices currently are available and are being tested in football	Energy detection devices embedded in helmets, or the lining of helmets, may reliably detect the energy imparted to the helmet, but this may or may not reflect the energy imparted to the head because of independent movement of the helmet

(*continued*)

Table 3. (Continued)

Diagnostic test	*Positives*	*Concerns*
		(Guskiewicz et al., 2007); consideration should be given to devices embedded in ear plugs/phones or mouthguards, or attached directly to the head at the mastoid prominences
Serum biomarkers (see Table 4)	Targeted proteins from neural tissue are furthest along the development path, but endothelial proteins also are associated with TBI; metabolomics, transcriptomics, and unbiased proteomics are expected to reveal other protein and non-protein biomarker candidates, including several inflammatory molecules	Serum levels of some of the promising molecular biomarkers, especially those associated with the inflammatory response, can vary significantly with exposure to a myriad of environmental variables, such as sleep deprivation, diet, non-central nervous system injury, and medications

that are released very early after TBI will be most relevant to the early diagnosis, and particularly the field diagnosis, of mTBI (Table 4). The presence and concentration of the biomarkers should be correlated with MRI or DTI as the reference standard. Testing in a well-classified biomarker repository would be ideal, and would speed discovery of the most useful biomarkers. Any blood drawn from SMs should include a sample for research that is shipped to a biorepository for study.

A point-of-care device containing a panel of biomarker detection tests is needed. Pilot studies should be done to determine which biomarkers are most sensitive to mTBI, and detection systems for only those biomarkers should be loaded onto the panel of the field-deployable device. Ideally the device would be small, disposable, lightweight, and functional in harsh field conditions that include extremes of heat, wind, and sand.

Optimal design of mTBI diagnostics research programs

The general methodology to validate mTBI diagnostic tests should include an initial evaluation of the candidate test, or group of tests, in civilian or non-theater military adults (18–50

Table 4. Candidate Biomarkers of TBI Currently Being Investigated

Test	*Indication*	*Development need*
Ubiquitin C-terminal hydrolase 1 (UCHL-1; Hausmann et al., 1999)	Potential to predict brain injury	Validation in mTBI ongoing (ELISA); requires FDA approval
Glial fibrillary acidic protein (GFAP; Pelinka et al., 2004; Wiesmann et al., 2010)	Potential to predict injury to glia	Undergoing validation in humans; validation in mTBI ongoing (ELISA); requires FDA approval
S100[a] (Mussack et al., 2000; Stranjalis et al., 2004)	Potential to predict intracranial hemorrhage after mTBI	Needs validation in an mTBI population and FDA approval; not entirely specific to CNS injury
Myelin basic protein[a] (MBP; Mao et al., 1995)	Reported as a head-injury-associated protein	Requires further validation
Neuron-specific enolase[a] (NSE; Begaz et al., 2006; Stalnacke et al., 2004)	Reported as a head-injury-associated enzyme	Requires further validation
Copper and ceruloplasmin[a] (Dash et al., 2010)	Reported as head-injury associated	Requires further validation
Axonal marker (Saatman et al., 2010)	For axonal injury, the presumed signature of mTBI	Not yet identified
Others[a]	Inflammatory and endothelial, among others	ELISAs available; need to be tested in mTBI populations

[a]ELISA available for research testing.

Those biomarkers considered most promising for early mTBI diagnosis are listed first.

mTBI, mild traumatic brain injury; ELISA, enzyme-linked immunosorbent assay; FDA, U.S. Food and Drug Administration; CNS, central nervous system.

years of age), with most if not all having been injured within 2 h. The study should focus on subjects very similar to those serving in the military, and where possible, should include a similar degree of sleep deprivation, stress, pharmacology (e.g., energy supplements and sleep aids), and diet. In many ways collegiate and professional athletes would be ideal civilian subjects. A group of new military recruits at risk for concussion during their training, such as airborne units, or special operations breecher trainees, might also be ideal for the initial evaluation of candidate tests. In some ways their environment is similar to in-theater circumstances, with high stress and limited sleep.

Initial validation of the candidate tests would be the clinical diagnosis based on a physical and cognitive evaluation performed by a trained physician, and based on a structured collateral history provided by both the patient and an SM from the unit who witnessed the event, or the commanding officer. This validating assessment would be done within 24–72 h of the injury, whenever possible. Validation should also include a comparison of 6-month and/or 1-year post-injury outcomes with baseline measurements to determine which acute diagnostic tools predicted post-concussive syndrome. Imaging validation should be included in the long-term assessment, and consist of a repeat MRI (DTI) on a system comparable to the pre-deployment MRI, to detect and quantify obvious traumatic lesions that were not previously apparent.

Age-, gender-, and occupation-matched controls should be included, as well as control subjects with non-CNS injuries, such as orthopedic injuries. Those tests found to be most promising in this first-phase non-combat setting must then be evaluated in-theater, because the blast environment may have unique features that affect test performance. The performance of most diagnostic tests, and particularly those that are most sensitive to mTBI, is likely to depend on the environment in which they will be used. For example, stress, some foods, and stimulants or other medications can significantly influence blood levels of several candidate biomarkers (Holtkamp et al., 2008; Kochanek et al., 2008).

The systematic comparison of candidate diagnostic tests is estimated to require 1000 subjects for baseline (pre-deployment) testing, although a power analysis will be necessary to confirm this number. The study should focus on high-risk service members with an assumed 15% chance of concussion within 1 year. If two-thirds of the subjects were likely to have complete datasets, and only 15% of the original 1000 subjects with pre-deployment testing had a concussion, then a minimum goal would be to have complete datasets in 100 service members. It is estimated that this is the minimum number of subjects that would allow for sufficient scientific rigor and the potential for strong validation. Consideration was given to an initial study of a cohort of civilian subjects enrolled at U.S. trauma centers. However, it ultimately was determined that the demographic characteristics and injury mechanisms for active duty service members in-theater were significantly different than for civilian TBI patients, so findings of a civilian study would not adequately predict what tests would be valid or practical in the military setting.

Baseline testing should be done in all study subjects, and should include the following: cognitive testing using a standard NCAT; blood, urine, and/or saliva tests for brain biomarkers and DNA genotyping (a current focus would be the APO-E genotype); EEG obtained using a field-deployable device; a test for autonomic instability such as heart rate monitoring variability or pupillometry (baseline/orthostatic and exertional); and DTI and conventional MRI with a focus on T2 sequences should also be obtained (Holli et al., 2010a, 2010b; Niogi and Mukherjee, 2010). A virtual reality (VR) performance test with ecological validation (e.g., shooting games and other military-specific scenarios with and without exertional testing) might also be considered (Parsons et al., 2008).

In order to identify the best field-deployable diagnostic tools for mTBI, acute post-injury testing should include a head-to-head comparison of newly developed and currently available measurement tools and technologies. Any new tools should be compared to the MACE, because it is currently used by medics and corpsmen in-theater to evaluate all SMs suspected of having a TBI. Comparison of the MACE with alternative assessment tools, such as the Sport Concussion Assessment Tool–Second Edition (SCAT2), should be considered as a possible research protocol (McCrory et al., 2009). Core components of SCAT2, such as assessment for post-trauma amnesia, standardized rating of symptoms, a brief neurological exam, and a cognitive screening test, are all similar to the MACE. In addition, SCAT2 includes a test for balance/postural stability. It is noteworthy that in the JAMA article upon which the MACE is based, McCrea and associates concluded that a test of postural stability should be included in the optimal concussion evaluation (McCrea et al., 2003). In civilians, sports-related concussion is frequently observed to have a negative effect on postural control. A significant correlation between self-reported symptoms, neurocognitive functioning, and abnormal postural control has been clearly defined (Broglio and Puetz, 2008). Moreover, injury to the vestibular system is increasingly recognized as a common sequela of blast injuries suffered by SMs in OIF/OEF (Scherer and Schubert, 2009).

Other candidate studies are a repeat, post-injury NCAT evaluation. The same NCAT used for baseline testing must also be used for post-injury testing.(Schatz and Putz, 2006). Resting and orthostatic EEG, resting and exertional VR performance testing, blood biomarkers, one or more tests of autonomic instability (e.g., heart rate and pupillometry), eye tracking, and energy sensor data also are tests that should be evaluated. It is important that energy-sensing technology be developed for direct contact with the head (e.g., embedded in the mouthguard or attached to a mastoid prominence), because studies of football players with helmet sensors have not found a clear relationship between head impact biomechanics and symptom severity, postural stability, or neuropsychological function (Guskiewicz et al., 2007). Where feasible, portable VR testing with combat- or theater-specific tasks may provide the most effective means of determining when the SM is ready for return to duty.

Summary and Conclusions

Diagnostic tests for mTBI that are currently considered most promising for evaluation over the next 2–3 years, and most likely to inform the best combination of tests for the early diagnosis of mTBI, are tests of pupil reaction, postural stability, and visual tracking, as well as biomarkers in blood, saliva, or urine, NIRS, and EEG or ERP. With biomarkers, the

challenge will be to identify those proteins or enzymes that appear very early after TBI, and to develop the field-deployable technology that can detect the very low levels of the biomarker that might be expected with mTBI. Testing of these diagnostic modalities should include the use of an energy sensor, preferably one that is attached to the head and is capable of transferring information to a laptop or personal digital assistant. Studies of combinations of diagnostic tools should evaluate aspects of the mTBI that are physiologically or pathologically different, and might include the following combinations:

- Biomarkers, NIRs, and EEG
- Biomarkers, MACE, and pupillometry or eye tracking
- NCAT, postural stability, and MACE
- Quantitative EEG/ERP, MACE, NCAT, and postural stability
- Biomarkers, MACE, and quantitative EEG/ERP

Eventually, these studies must be shown to correlate well with the symptom characteristics of mTBI to be universally accepted. It is anticipated that certain tests will diagnose mTBI better than others, and that those tests will be ranked accordingly. The study should include an interim analysis, and diagnostic tests that are not sensitive and specific for mTBI should be eliminated. It also is anticipated that certain combinations of tests will be most accurate. Ultimately, the study is expected to show which subset of the tests is most appropriate for the early and rapid diagnosis of mTBI. In many cases, such as with MRI, pre-deployment testing may not be necessary once the tests are validated.

The goal should be for post-injury testing to take no more than 15 min to complete. Specialized testing devices and equipment will need to be provided, as well as staff that are familiar with and trained to use the devices/tests. Consideration should be given to alternative locations of administering tests, such as outside versus inside, and within a vehicle such as a mine-resistant ambush-protected vehicle. Platforms for containing and administering the tests also should be contemporary, and include smartphone applications.

Technical and administrative concerns that delay clinical research in the military also must be aggressively and effectively addressed up front if critical research goals are to be met within a 2- to 3-year time span. Ideally, a government liaison should be available to facilitate approval of new diagnostic tests or systems by the FDA. Under normal circumstances it is not uncommon for the FDA approval process of new diagnostic devices to take a year or more. In addition, informed consent and logistical issues must be effectively addressed to enable research in-theater. Current protocols involve a multi-level institutional review board approval process that takes months to complete. Research resources in-theater should also be carefully assessed, and where necessary enhanced. This may include designation of 4–5 Role II or Role III military treatment facilities (MTFs) as clinical research sites, and the deployment of a dedicated neurotrauma research team that can temporarily attach to MTFs or forward operating bases.

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References

Barr, W.B., and McCrea, M. (2001). Sensitivity and specificity of standardized neurocognitive testing immediately following sports concussion. J. Int. Neuropsychol. Soc. 7, 693–702.

Begaz, T., Kyriacou, D.N., Segal, J., and Bazarian, J.J. (2006). Serum biochemical markers for post-concussion syndrome in patients with mild traumatic brain injury. J. Neurotrauma 23, 1201–1210.

Bergsneider, M., Hovda, D.A., McArthur, D.L., Etchepare, M., Huang, S.C., Sehati, N., Satz, P., Phelps, M.E., and Becker, D.P. (2001). Metabolic recovery following human traumatic brain injury based on FDG-PET: time course and relationship to neurological disability. J. Head Trauma Rehabil. 16, 135–148.

Broglio, S.P., and Puetz, T.W. (2008). The effect of sport concussion on neurocognitive function, self-report symptoms and postural control : a meta-analysis. Sports Med. 38, 53–67.

Carroll, L.J., Cassidy, J.D., Peloso, P.M., Borg, J., von Holst, H., Holm, L., Paniak, C., and Pepin, M. (2004). Prognosis for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J. Rehabil. Med. 43 Suppl., 84–105.

Casscells, S.W. (2007). *Traumatic Brain Injury: Definition and Reporting*. HA Department of Defense: Washington, D.C.

Dash, P.K., Redell, J.B., Hergenroeder, G., Zhao, J., Clifton, G.L., and Moore, A. (2010). Serum ceruloplasmin and copper are early biomarkers for traumatic brain injury-associated elevated intracranial pressure. J. Neurosci. Res. 88, 1719–1726.

Defense and Veterans Brain Injury Center/Armed Forces Health Surveillance Center (DVBIC/AFHSC). (2010). http://www.dvbic.org/TBI-Numbers.aspx.

Ellemberg, D., Henry, L.C., Macciocchi, S.N., Guskiewicz, K.M., and Broglio, S.P. (2009). Advances in sport concussion assessment: from behavioral to brain imaging measures. J. Neurotrauma 26, 2365–2382.

Giljohann, D.A., and Mirkin, C.A. (2009). Drivers of biodiagnostic development. Nature 462, 461–464.

Giza, C.C., and Hovda, D.A.. (2001). The neurometabolic cascade of concussion. J. Athl. Train. 36, 228–235.

Guskiewicz, K.M., Bruce, S.L., Cantu, R.C., Ferrara, M.S., Kelly, J.P., McCrea, M., Putukian, M., and Valovich McLeod, T.C. (2004). National Athletic Trainers' Association Position Statement: Management of Sport-Related Concussion. J. Athl. Train. 39, 280–297.

Guskiewicz, K.M., Mihalik, J.P., Shankar, V., Marshall, S.W., Crowell, D.H., Oliaro, S.M., Ciocca, M.F., and Hooker, D.N. (2007). Measurement of head impacts in collegiate football players: relationship between head impact biomechanics and acute clinical outcome after concussion. Neurosurgery 61, 1244–1252.

Hausmann, R., Kaiser, A., Lang, C., Bohnert, M., and Betz, P. (1999). A quantitative immunohistochemical study on the time-dependent course of acute inflammatory cellular response to human brain injury. Int. J. Legal Med. 112, 227–232.

Holli, K.K., Harrison, L., Dastidar, P., Waljas, M., Liimatainen, S., Luukkaala, T., Ohman, J., Soimakallio, S., and Eskola, H. (2010a). Texture analysis of MR images of patients with mild traumatic brain injury. BMC Med. Imaging 10, 8.

Holli, K.K., Waljas, M., Harrison, L., Liimatainen, S., Luukkaala, T., Ryymin, P., Eskola, H., Soimakallio, S., Ohman, J., and Dastidar, P. (2010b). Mild traumatic brain injury: tissue texture analysis correlated to neuropsychological and DTI findings. Acad. Radiol. 17, 1096–1102.

Holtkamp, K., Buhren, K., Ponath, G., von Eiff, C., Herpertz-Dahlmann, B., Hebebrand, J., and Rothermundt, M. (2008). Serum levels of S100B are decreased in chronic starvation and normalize with weight gain. J. Neural. Transm. 115, 937–940.

Iverson, G.L., Kaarto, M.L., and Koehle, M.S. (2008). Normative data for the balance error scoring system: implications for brain injury evaluations. Brain Inj. 22, 147–152.

Kochanek, P.M., Berger, R.P., Bayir, H., Wagner, A.K., Jenkins, L.W., and Clark, R.S. (2008). Biomarkers of primary and evolving damage in traumatic and ischemic brain injury: diagnosis, prognosis, probing mechanisms, and therapeutic decision making. Curr. Opin. Crit. Care 14, 135–141.

Mao, Q., Chen, J., Li, N., Li, C., Mao, B., Wang, R., and Wu, G. (1995). The value of serum myelin basic protein in assessment of severity of acute closed head trauma. Hua Xi Yi Ke Da Xue Xue Bao 26, 135–137.

McCrea, M., Guskiewicz, K.M., Marshall, S.W., Barr, W., Randolph, C., Cantu, R.C., Onate, J.A., Yang, J., and Kelly, J.P. (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. JAMA 290, 2556–2563.

McCrea, M., Hammeke, T., Olsen, G., Leo, P., and Guskiewicz, K. (2004). Unreported concussion in high school football players: implications for prevention. Clin. J. Sport Med. 14, 13–17.

McCrory, P., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., and Cantu, R. (2009). Consensus statement on concussion in sport: the Third International Conference on Concussion in Sport held in Zurich, November 2008. Phys. Sportsmed. 37, 141–159.

mTBI Working Group. (2009). VA/DoD Clinical practice guideline for management of concussion/mild traumatic brain injury.

Mussack, T., Biberthaler, P., Wiedemann, E., Kanz, K.G., Englert, A., Gippner-Steppert, C., and Jochum, M. (2000). S-100B as a screening marker of the severity of minor head trauma (MHT)—a pilot study. Acta Neurochir. Suppl. 76, 393–396.

Niogi, S.N., and Mukherjee, P. (2010). Diffusion tensor imaging of mild traumatic brain injury. J. Head Trauma Rehabil. 25, 241–255.

Parsons, T.D., Silva, T.M., Pair, J., and Rizzo, A.A. (2008). Virtual environment for assessment of neurocognitive functioning: virtual reality cognitive performance assessment test. Stud. Health Technol. Inform. 132, 351–356.

Pelinka, L.E., Kroepfl, A., Leixnering, M., Buchinger, W., Raabe, A., and Redl, H. (2004). GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome. J. Neurotrauma 21, 1553–1561.

Saatman, K.E., Creed, J., and Raghupathi, R. (2010). Calpain as a therapeutic target in traumatic brain injury. Neurotherapeutics 7, 31–42.

Schatz, P., and Putz, B.O. (2006). Cross-validation of measures used for computer-based assessment of concussion. Appl. Neuropsychol. 13, 151–159.

Scherer, M.R., and Schubert, M.C. (2009). Traumatic brain injury and vestibular pathology as a comorbidity after blast exposure. Phys. Ther. 89, 980–992.

Stalnacke, B.M., Tegner, Y., and Sojka, P. (2004). Playing soccer increases serum concentrations of the biochemical markers of

brain damage S-100B and neuron-specific enolase in elite players: a pilot study. Brain Inj. 18, 899–909.

Stranjalis, G., Korfias, S., Papapetrou, C., Kouyialis, A., Boviatsis, E., Psachoulia, C., and Sakas, D.E. (2004). Elevated serum S-100B protein as a predictor of failure to short-term return to work or activities after mild head injury. J. Neurotrauma 21, 1070–1075.

Tanielian, T.J.L., Schell, T.L., Marshall, G.N., Burnam, M.A., Eibner, C., Karney, B.R., Meredith, L.S., Ringel, J.S., Vaiana, M.E., and the Invisible Wounds Study Team. (2008). Invisible Wounds, Mental Health and Cognitive Care Needs of America's Returning Veterans, Rand Center for Military Health Policy Research, Santa Monica, California.

Tisdall, M.M., and Smith, M. (2007). Multimodal monitoring in traumatic brain injury: current status and future directions. Br. J. Anaesth. 99, 61–67.

van Rossem, K., Garcia-Martinez, S., De Mulder, G., Van Deuren, B., Engelborghs, K., Van Reempts, J., and Borgers, M. (1999). Brain oxygenation after experimental closed head injury. A NIRS study. Adv. Exp. Med. Biol. 471, 209–215.

Wiesmann, M., Steinmeier, E., Magerkurth, O., Linn, J., Gottmann, D., and Missler, U. (2010). Outcome prediction in traumatic brain injury: comparison of neurological status, CT findings, and blood levels of S100B and GFAP. Acta Neurol. Scand. 121, 178–185.

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